Editorial

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Diagnosing cirrhosis non-invasively: Sense the stiffness but don't forget the nodules!

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Liver cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury [1]. Cirrhosis is often asymptomatic and unsuspected until complications such as liver failure, portal hypertension, and hepatocellular carcinoma occur. For instance, in patients with compensated viral cirrhosis, the leading form worldwide, the annual incidence rates of decompensation, hepatocellular carcinoma, and death are approximately 4%, 3%, and 3%, respectively [2]. Thus, early diagnosis of cirrhosis is important for patients with chronic liver disease, because it both triggers screening for hepatocellular carcinoma and esophageal varices, and enables initiation of specific measures or treatment to prevent disease progression, such as alcohol abstinence; antiviral therapy for viral hepatitis; lifestyle changes in NASH; steroid therapy for auto-immune hepatitis; and phlebotomy for hemochromatosis.

Histological examination of a liver specimen obtained by biopsy has traditionally been considered the reference method for diagnosing cirrhosis [3]. Liver biopsy may also be important for establishing the cause of cirrhosis in up to 20% of patients with an unknown etiology [1]. However, its diagnostic accuracy has been questioned, owing to sampling errors and intra- and inter-observer variability, that may lead to an underestimation of cirrhosis [4]. In addition, biopsy is an invasive and painful procedure associated with rare but potentially life-threatening complications. Several non-invasive approaches have therefore been developed, including serum biomarkers and imaging techniques such as ultrasonography and, more recently, liver stiffness measurement (LSM) by means of transient elastography (TE). Ultrasonography is usually the first imaging technique to be used in the clinical workup of patients with suspected liver diseases, as it is simple, non-invasive, inexpensive, and widely available. Features such as caudate lobe hypertrophy and nodularity of the liver surface are suggestive of cirrhosis. However, although their specificity is high (91% and 95%, respectively), their sensitivity is not good enough (41% and 54%, respectively) to diagnose cirrhosis with confidence in clinical practice [5]. In addition, ultrasonographic findings are highly operator-dependent. Conversely, TE is a reproducible, operator-independent, and user-friendly technique that can be performed at the bedside with immediate results [6]. Liver stiffness has been shown to correlate with hepatic fibrosis stages and to have excellent diagnostic accuracy for cirrhosis [7–10]. When compared to current biomarkers and routine blood tests, TE emerges as the most accurate non-invasive method for early detection of cirrhosis in patients with chronic hepatitis C [11], and it is "the test to be beaten" for those developing alternative methods [12]. However, the respective values of ultrasonography and TE for the diagnosis of cirrhosis had not yet been directly compared.

The study by Berzigotti et al. [13] in the current issue of the *Journal of Hepatology* is therefore particularly welcome. The authors prospectively compared the diagnostic value of TE and high-resolution ultrasound evaluation of the left lobe liver surface (LLS) in 90 patients to clinical suspicion of cirrhosis and a strong existing differential diagnosis. Cirrhosis was present in around half the patients, as shown by histological examination (84%) or by clinically significant portal hypertension (hepatic venous pressure gradient: HVPG $\geqslant$10 mm Hg) and compatible clinical and laboratory data. The main finding is that LLS and TE had similar diagnostic accuracy (respective areas under the ROC curve: 0.88 and 0.91), although LLS was better at ruling in cirrhosis (positive likelihood ratio: 11.15) while TE was better at ruling it out (negative likelihood ratio: 0.08).

LLS examination is rapid (less than 5 min) and can, like TE, be performed at the bedside with immediate, semi-quantitative results (smooth, irregular, or nodular liver surface). In order to minimize observer-dependency, the authors used a novel method based on computerized post-processing of the ultrasound images, which allows LLS length to be determined in a standardized segment (qLLS) with excellent intra- and inter-observer reproducibil-

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Abbreviations: LSM, liver stiffness measurement; TE, transient elastography; LLS, left lobe liver surface; HVPG, hepatic venous pressure gradient.

ity. Semi-quantitative assessment of LLS was superior to qLLS for diagnosing and excluding cirrhosis but left a substantial number of patients with indeterminate results. A significant number of indeterminate cases was also obtained with TE, because of the use of two different diagnostic cut-offs (<12 kPa for the absence and >18 kPa for the presence of cirrhosis). This use of two cut-offs is questionable and probably unfair towards TE, although diagnostic performance did not improve when a single "optimal" cut-off (13 kPa) was used [10]. With HVPG or liver biopsy as the reference standard, the majority of these patients with indeterminate findings proved to be free of cirrhosis but to have heterogeneous hepatic status, ranging from normal to cardiac congestive liver, which brings us to the second point: are these findings applicable to other populations? The study population consisted of a relatively small number of highly selected patients referred to a very specialized tertiary center. Also, HVPG measurement requires a high degree of expertise and is not part of the routine management of patients with suspected liver disease in most centers. Despite these limitations, this study provides important data that can be translated immediately into clinical practice. As the authors emphasize, it is important to conduct clinical studies of patients typically encountered in day-to-day clinical care. So far, most of the data we have on non-invasive methods originate from cohorts of patients with chronic hepatitis C, and these methods are not yet widely used in routine practice [14].

A particularly interesting finding of this study is the fact that, despite similar performance for diagnosing cirrhosis, the concordance between the TE and LLS was only moderate. This may be due partly to the fact that TE is applied to the right lobe and LLS to the left lobe. However, the most likely explanation is that TE and LLS evaluate two different, albeit complementary, characteristics of cirrhosis: TE senses liver stiffness, while LLS visualizes nodules. It is therefore not surprising that diagnostic accuracy improves when the two methods are combined. Such a combined approach has already been suggested to increase diagnostic accuracy in the absence of a "perfect" gold standard, which is the case for liver biopsy [15]. Another advantage is the complementary applicability of TE and LLS. Indeed, in the study by Berzigotti et al., the applicability of LLS was much better than that of TE, but the TE failure rate (15%) was higher than usually reported (5%), likely owing to the inclusion of patients with ascites. However, in our experience with more than 13,000 examinations over a 5-year period, TE is not applicable in nearly one out of five patients [16], owing either to failure (no valid shot) (4%) or unreliable results (17%: valid shots <10, IQR/LSM >30% and success rate <60%). The principal reasons are obesity (particularly large waist circumference) and limited operator experience. Despite these limitations, TE may still have other advantages over LLS, such as for monitoring disease progression. Liver stiffness shows an excellent correlation with HVPG values below 10–12 mm Hg [17,18]. Although these findings need to be confirmed in larger independent studies, they suggest that LSM may be useful for detecting clinically significant portal hypertension and, thus, for further sub-classifying compensated cirrhosis [19]. Berzigotti et al. did not investigate the accuracy of TE for diagnosing clinically significant portal hypertension (as measured by HVPG), but this was beyond the scope of their work. Finally, liver stiffness may have prognostic value in patients with cirrhosis, suggesting that TE could be used as a rapid screening tool for allocating cirrhotic patients to specific risk categories. Longitudinal studies are now needed to determine whether single or serial TE examinations are predictive of decompensation, further decompensation, or even death [20].

In conclusion, this important study suggests that cirrhosis can be diagnosed rapidly in clinically doubtful cases, based on the simultaneous presence of increased liver stiffness and nodules, as detected by two simple non-invasive methods available at the bedside. Because of its specific setting, the findings of this study need to be confirmed in larger samples and in other populations at risk of cirrhosis. The current challenge for non-invasive methods is to detect cirrhosis in asymptomatic patients with chronic liver diseases, in routine clinical practice.

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